## REMARKS

Claims 1-8 are all the claims pending in the application; claims 1-6 and 8 have been cancelled; claim 7 has been amended; new claims 9-13 have been added.

Claim 7 has been amended to correct obvious grammatical errors and more fully comply with U.S. practice regarding claim drafting.

New claims 9-13 are fully supported by the specification, see, for example, page 7, lines 4-21; page 10, lines 4-8; page 11, line 25 - page 12, line 3; page 14, lines 3-5.

Accordingly, no new matter has been added and entry of the amendment is earnestly solicited.

### I. Objection to Amendment of the Specification

At page 2 of the Office Action, first paragraph, the Examiner objects to the amendment of the specification under 35 U.S.C. §132 as introducing new matter.[1]

The Examiner states that the change of the units from "mg/kg" to "mg" at page 14, lines 5 and 12, is not a minor amendment and instead introduces new matter that is not supported by the specification.

In response, Applicants respectfully assert that there is clear support for the amendment. As taught at multiple locations in the specification (page 7, line 20; page 15, line 15; page 20, line 22; page 21, line 16), administration of Compound A is referred to as being a "mg" dosage per day, and not a "mg/kg" dosage per day. Thus, the recitation of "mg/kg" is an obvious error.

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[1] While the Examiner states that the Amendment was filed September 24, 2001, Applicants believe that the Examiner is referring to the Preliminary Amendment filed June 25, 2001.

Furthermore, based on the context in which the discussion takes place at page 14 of the specification, it is clear that a range of dosages is being disclosed and that if in each instance the dosages of the first two ranges are correctly reported (in "mg"), then the narrowest dosage range should also be reported in "mg."

Applicants thus request reconsideration and withdrawal of this objection.

**II. Warning**

At page 2 of the specification, last paragraph, the Examiner asserts that claims 1 and 3 are substantial duplicates of each other, as are claims 2 and 4.

In response, Applicants note that claims 1, 2, 3 and 4 have been cancelled from the Application. As a result, Applicants respectfully assert that the warning is moot, and request reconsideration and withdrawal of the warning.

**III. Rejection of claims under 35 U.S.C. §112**

A. At page 3 of the Office Action, last paragraph, the Examiner rejects claims 1 and 3 under 35 U.S.C. §112, first paragraph, as being non-enabled.

In response, Applicants note that claims 1 and 3 have been cancelled from the Application. As a result, Applicants respectfully assert that the rejection is moot, and request reconsideration and withdrawal of the rejection.

B. At page 5 of the Office Action, first full paragraph, the Examiner rejects claims 1, 3 and 8 under 35 U.S.C. §112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In response, Applicants note that claims 1, 3 and 8 have been cancelled from the Application. As a result, Applicants respectfully assert that the rejection is moot, and request reconsideration and withdrawal of the rejection.

**IV. Rejection of claims under 35 U.S.C. §102**

A. At page 6 of the Office Action, first full paragraph, the Examiner rejects claims 1 and 3 under 35 U.S.C. §102(b) as being anticipated by Shipman et al. (Leukemia and Lymphoma).

In response, Applicants note that claims 1 and 3 have been cancelled from the Application. As a result, Applicants respectfully assert that the rejection is moot, and request reconsideration and withdrawal of the rejection.

B. At page 6 of the Office Action, fourth full paragraph, the Examiner rejects claims 2 and 4-6 under 35 U.S.C. §102(b) as being anticipated by Isomura et al.

In response, Applicants note that claims 2 and 4-6 have been cancelled from the Application. As a result, Applicants respectfully assert that the rejection is moot, and request reconsideration and withdrawal of the rejection.

**V. Rejection of claims under 35 U.S.C. §103**

At page 7 of the Office Action, first paragraph, the Examiner rejects claims 7 and 8 under 35 U.S.C. §103(a) as being unpatentable over Isomura et al. in view of Shipman et al.

The Examiner asserts that Isomura et al. teaches that heterocyclic bisphosphonic acid compounds, including 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bisphosphonic acid,

can be blended with pharmaceutically-acceptable carriers to form medical compositions suitable for oral administration (col. 7, lines 7-19; col. 9, Example 5).

The Examiner admits that Isomura et al. does not expressly teach that 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bisphosphonic acid is useful in a method of treating bone lesion in multiple myeloma.

However, the Examiner asserts that Shipman et al. teaches that potent bisphosphonates are useful in treating multiple myeloma, and it would have been obvious to one of ordinary skill in the art to employ 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bisphosphonic acid in a method of treating bone lesions in multiple myeloma.

In response, Applicants note that claim 8 has been cancelled and therefore contend that the rejection with regard to claim 8 is moot.

As to claim 7, Applicants assert the following.

(1) It has been known for some time that bisphosphonates ("BPs") are effective in the treatment of bone lesions. Furthermore, 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bisphosphonic acid (hereinafter referred to as "Compound A") is a BP. However, the present inventors have newly discovered an additional property of Compound A, namely, its ability to effectively treat multiple myeloma ("MM").

Indeed, Compound A is a new type of compound in that, in a patient suffering from MM, the compound has the effect of both suppressing bone resorption and ameliorating MM (i.e., anticancer activity) when administered at the same dosage. Accordingly, through the administration of a compound having both of these activities, namely, Compound A, the present

invention achieves for the first time the treatment of bone lesions and MM in a patient with MM. In this regard, the present invention is not taught or suggested by the references cited by the Examiner.

As shown in Example 4 of the instant specification (page 20, line 15 - page 21, line 11), a 3 mg/day oral administration of Compound A considerably decreased the cancer marker in addition to the effect of suppressing bone lesions. That is, Compound A is the first BP compound which has been confirmed to have both an effect of treating bone resorption and an effect of treating multiple myeloma in the MM patient.

In contrast, Isomura merely discloses that Compound A has a bone resorption effect. Isomura does not teach or suggest the dual properties of improving bone lesions and effective treatment multiple myeloma in the MM patient. Accordingly, Isomura does not teach or suggest the present invention which can treat bone lesions accompanying MM and MM itself by administering, to a MM patient, Compound A in an amount sufficient for both suppressing bone resorption accompanying multiple myeloma and inhibiting multiple myeloma.

With respect to the Shipman reference, the Examiner states "Shipman et al. teaches that clodronate and pamidronate are useful in treating multiple myeloma." However, at page 131, Table 1, it is merely shown that the clinical experiments using these compounds on the MM patient showed an effect to improve bone lesions and survival. There is no disclosure concerning the treatment of MM *per se*. Moreover, a reference which disputes the anticancer effect of pamidronate is cited at page 135 (col. 1, lines 17-21) of Shipman, wherein it is stated that "[p]amidronate has been used in a murine model of myeloma, and although no effect on tumour

growth was demonstrated, there was evidence of a cytotoxic effect of the bisphosphonate within the bone marrow."

In addition, although the Examiner states "Shipman et al. teaches that a heterocyclic bisphosphonate, residronate, has a relative potency of 5000," importantly, at page 135 (col. 1, line 21 - col. 2, line 2), a reference (Garrett et al.) which denies the anticancer effect is cited "[t]he potent anti-resorptive bisphosphonate, risedronate, has also been used in a murine model of myeloma; however, although there was a clear reduction in bone destruction, no effect on tumour burden was noted." Thus, Garrett et al. discloses the fact that risedronate, which has a high potency, did not have an effect on the treatment of MM by the *in vivo* animal test. Accordingly, Garrett et al. teaches against MM treatment activity in the MM patient with respect to even risedronate which has a high potency, instead showing negative results in the known animal model experiments, to say nothing of clodronate and pamidronate.

Accordingly, Shipman et al. does not teach or suggest that potent BPs, such as clodronate and pamidronate, are effective for treatment of MM. Furthermore, the references cited therein teach against the use of BPs for the treatment of MM. Because Shipman et al. does not teach or suggest a BP which has the dual effect of treating bone resorption and MM in the MM patient, the present invention which administers a compound having both of these effects is not disclosed or suggested, and thus is unobvious over the references cited by the Examiner.

(2) The treatment method of claims 7 and 10 relates to the method of treating bone lesions accompanying MM in a MM patient, based on the excellent effects of Compound A to

suppress bone resorption and to treat MM. Accordingly, the invention has unexpectedly superior effects and is thus unobvious.

(3) The treatment method of claims 9 and 11 is not disclosed in the references. Accordingly, it is apparent that the invention is unobvious.

(4) The Examiner states that "certain potent bisphosphonates are useful in treating MM" and alleges that this is motivation to employ Compound A in a method of treating bone lesions in multiple myeloma and that, because Compound A has a structure which is similar to that of risedoronate, it "would be reasonably expected to be useful in a method of treating bone lesions in MM."

Applicants assert, however, that Compound A has an imidazo pyridine skeleton which is a fused heterocyclic ring. It is readily apparent that Compound A has a structure which is quite different from the pyridine derivatives of the prior art and is not homologous to the pyridine derivatives. It is also clear from page 131, Table 1 of Shipman et al., that the structure of BPs, other than the phosphonic acid structure, has a great influence on the activities of BPs. It is well known to one skilled in the art that, in addition to the main activity, additional activities including side-effects and bioavailability, are greatly changed by the alteration of the structure. Accordingly, without actually conducting experiments, it is impossible to know what treatment effects will result from the administration of Compound A to the MM patient.

Accordingly, Applicants respectfully assert that the effect of Compound A on the MM patient is not taught or made obvious from the references disclosing the treatment of bone lesions in the MM patient using known BPs. While the prior art suggests that BP would not be

functional in the treatment of MM, the present inventors have shown that Compound A is effective in the treatment of both bone lesions and MM. In addition, the structural differences between Compound A and known BPs further support the non-obviousness of the present invention.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection.

## VI. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Applicant hereby petitions for any extension of time which may be required to maintain the pendency of this case, and any required fee, except for the Issue Fee, for such extension is to be charged to Deposit Account No. 19-4880.

Respectfully submitted,

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## APPENDIX

## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**IN THE CLAIMS:**

**Claims 1-6 and 8 are canceled.**

**The claims are amended as follows:**

7. (amended) A method of treating bone lesions accompanying ~~in~~ multiple myeloma which comprises administering to a patient suffering from multiple myeloma ~~an effective amount of~~ 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-bisphosphonic acid or a ~~its~~ salt thereof in an amount sufficient for ~~having~~ both ~~of an effect of~~ suppressing bone resorption accompanying multiple myeloma and ~~an effect of~~ inhibiting multiple myeloma.

**Claims 9-13 are added as new claims.**